

Concurrent splenic lymphangiomas and Proteus syndrome

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ABSTRACT

نستعرض هنا حالة مريضة تبلغ من العمر 37 عام مصابة بمتلازمة المتقلبة وشخصت بطحال متضخم عديم الأعراض. أظهر الفحص النسيجي ورم وعائي لمفي. نصف في هذا التقرير الصلة بين المرضين في سكان الشرق الأوسط. كما تمت مناقشة التشخيص والمرض في هذا التقرير.

A 37-year-old female presented with Proteus syndrome and was found to have an asymptomatic enlarged spleen. Pathology confirmed splenic lymphangiomas. We describe an association of these 2 disorders in the Middle Eastern population. Diagnosis and pathogenesis are discussed in this case report.

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Proteus syndrome is a rare congenital disorder.¹ It was named after the Greek god Proteus, meaning 'The Polymorphous,' for he could avoid capture by altering his shape.² It can manifest usually as progressive skeletal abnormalities including asymmetric overgrowth, macrodactyly, scoliosis, and limb length discrepancy followed by soft tissue anomalies namely fatty, muscular, lymphatic,³ and vascular malformations. Visceral malformations are rare including splenomegaly.¹ In this case report, we highlight the rare association of this syndrome with lymphangiomas in the Middle-Eastern population.

Case Report. A 37-year-old female, presented to King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia with asymmetrical enlargement of the hands and feet, and a large asymptomatic abdominal mass for the past 3 years with a differential diagnosis of polycystic/neoplastic spleen. Her past surgical history included a removal of a cyst from the anterior chest wall. Physical examination revealed bilateral macrodactyly (Figures 1A & 1b), and asymmetric enlargement of the digits of the hands and feet along with swelling of the limbs (more noticeable in the left limb). Abdominal examination revealed a small wall nodule and a left upper quadrant massive hard mass to the level of the umbilicus. A CT scan (Figures 2A, 2B & 2C) confirmed splenomegaly (23x21x13 cm) with a provisional diagnosis of hemangioma/lymphangioma of the spleen. It was labeled as a 'wandering spleen' that had shifted anterior to mesentery but below the stomach and pancreas, along with portal and superior mesenteric vein aneurysmal dilatation. It also revealed bilateral cystic changes in the adrenals and a hepatic hemangioma of approximately 0.4 cm. Skeletal survey turned out to be unremarkable and the conclusion of Proteus Syndrome was reached in light of all the findings. Admission laboratory test were within normal limits. Her elective splenectomy was carried out as an open procedure. The post-op period was uneventful with a stable platelet count. The pathology report as follows indicated that the splenomegaly was a result of extensive involvement by lymphangiomas, and the abdominal wall biopsy came out to be an intradermal nevus.

Pathology report. The removed spleen was enlarged, weighing 1490 grams, and measured 22 x 17 x 11 cm.

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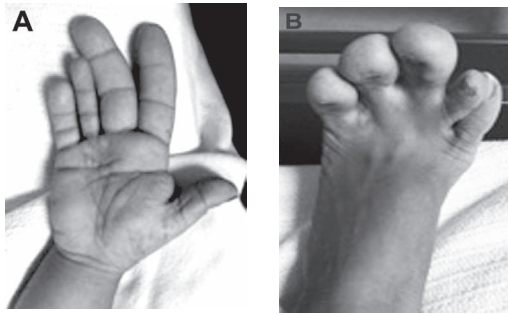


Figure 1 - The hypertrophied extremities of the A) hand, and B) foot of this particular patient.

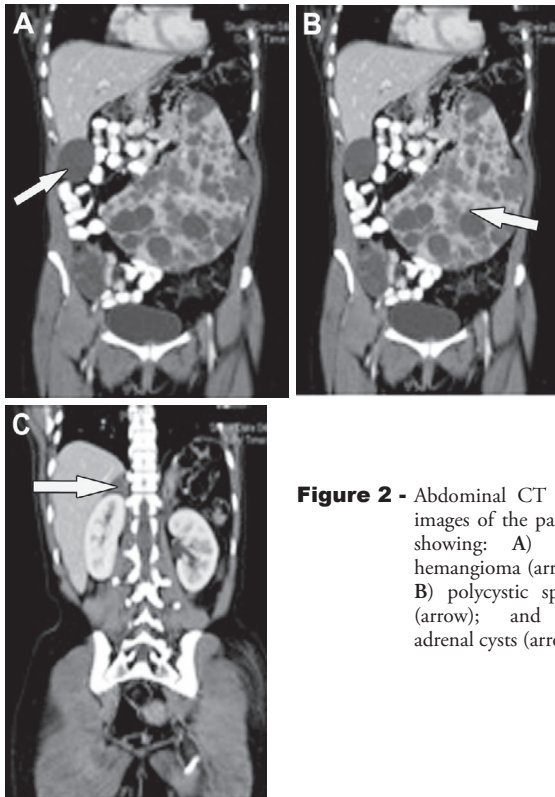


Figure 2 - Abdominal CT scan images of the patient showing: A) liver hemangioma (arrow); B) polycystic spleen (arrow); and C) adrenal cysts (arrow).



Figure 3 - Gross specimen of splenomegaly with capsular nodularity and parenchymal infiltration produced by cysts.

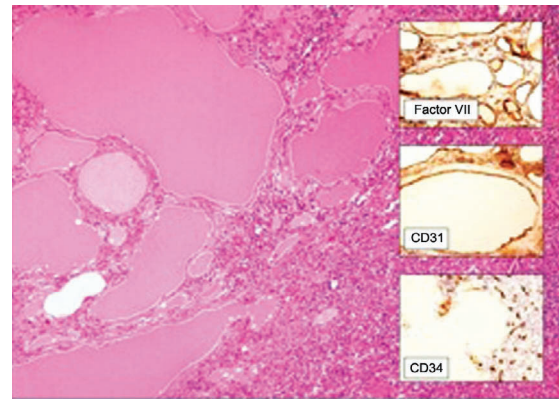


Figure 4 - Lymphangiomatosis in the spleen, forming chyle-filled cystic spaces within the splenic red pulp. Lining endothelial monolayer expresses Factor VIII and cluster of differentiation (CD)31 antigens, and lacks CD34, otherwise present in splenic microvasculature.

Sectioning revealed multiple cystic spaces throughout the splenic tissue, ranging in diameter from 0.7-5 cm (Figure 3). These spaces were typically filled with clear straw-colored fluid. Microscopic examination confirmed the extensive parenchymal replacement by communicating channels and cystically dilated spaces, filled with lymph, and with some foci of secondary hemorrhage. The spaces were lined by flat, non-descript endothelium without papillary proliferation or atypia, exhibiting immunopositivity for cluster of differentiation (CD)31 and Factor VIII, with absence of CD34 as shown in Figure 4. The remaining red pulp displayed fibrocongestive and reactive changes. The white pulp was inactive. The architecture and marker profile of this process establish a diagnosis of lymphangiomatosis, producing moderate splenomegaly. Vasoformative neoplasms (for example, littoral cell angioma, hemangioendothelioma, and so forth) are excluded on morphologic and phenotypic grounds.

Discussion. There are a few reported cases of Proteus syndrome, including Joseph Merrick or 'the elephant man' who was misdiagnosed as neurofibromatosis type 1, but later on was proven to have the Proteus syndrome in the early 20th century.⁴ Most of the cases showed the common symptoms of asymmetrical limb enlargement but only a few reported cases indicated visceral malformations including splenomegaly. According to the findings, a diagnostic criterion was drawn to categorize the patients with this disease and rule out any other differentials.^{1,4} The molecular pathogenesis of the Proteus syndrome has recently been elucidated. In

an initial series of 29 patients examined at the National Institutes of Health, 26 were found to have a mutation (c.49G→A, p. Glu17Lys) in the V-akt murine thymoma viral oncogene homolog 1 (AKT1) gene, encoding an enzyme involved in the regulation of cell proliferation and apoptosis.⁵ The AKT1 protein is a component of the phosphoinositide 3-kinase (PI3K)-AKT signaling pathway. Subsequent studies demonstrated the mutation in a larger cohort of patients; and revealed that the functional effect is to produce activation of AKT1 by increasing phosphorylation of the Ser473 and Thr308 residues. This somatic mutation in a single gene is transmitted to a subpopulation of descendant cells - resulting in mosaicism, and if found in all cells of the body, the mutation would be lethal. In murine models, activated forms of the gene yield a phenotype similar to that of the Proteus syndrome, with cutaneous hyperplasia, calcification of cartilage, and so forth.⁵

Our patient was a mild form of Proteus syndrome, and according to the criteria, she belonged to category B1 with the classical symptoms of macrodactyly, asymmetric limb enlargement, epidermal nevi, and visceromegaly. Although there have also been reported cases of Kasabach-Merritt syndrome associated with Proteus where patients exhibited features of disseminated intravascular coagulation with splenic hemangioma,⁶ our patient had no underlying hematological condition, and her syndrome was diagnosed due to the incidental finding of massive cystic splenomegaly, for which she was surgically treated. Subsequently, the histopathology indicated diffuse lymphangiomatosis as the cause of splenomegaly.

Lymphangiomatosis is a multi-system disorder due to congenital malformation of the lymphatic system. It is a condition marked by cysts resulting from an increase in the size and number of dilated lymphatic channels that have abnormal interconnections. In 65% of patients, there is affection of soft organs (mostly in the spleen, liver, and lungs), and the skeleton (long bones, pelvis,

skull, and vertebrae).⁷ Adrenal lymphangiomatosis, coexistence of cystic intra-abdominal lymphangiomas and diffuse venous hemangiomas in adult life are reported.^{8,9}

In conclusion, most cases of Proteus syndrome remains undiagnosed due to variable manifestations of this disease, which may overlap with other disorders, and the diagnosis is usually achieved on clinical evaluation and imaging studies. In this report however, the patient was treated only for the asymptomatic splenomegaly, and she was consequently diagnosed with lymphangiomatosis secondary to Proteus syndrome.

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